(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 May 2003 (08.05.2003)

PCT

(10) International Publication Number
WO 03/037379 A1

(51) International Patent Classification[7]: A61K 47/02, 31/00, 31/60, 31/165, 31/355, A61P 29/00, 39/06, 43/00

(21) International Application Number: PCT/EP02/07588

(22) International Filing Date: 6 July 2002 (06.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
101 53 078.1 30 October 2001 (30.10.2001) DE

(71) Applicant: **DEGUSSA AG** [DE/DE]; Bennigsenplatz 1, 40474 Düsseldorf (DE).

(72) Inventors: **HASENZAHL, Steffen**; Florscheidstrasse 23, 63477 Maintal (DE). **MEYER, Jürgen**; Grossostheimer Strasse 51, 63811 Stockstadt (DE). **HEYM, Jürgen**; Hainbühlstrasse 23, 63755 Hörstein (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/037379 A1

(54) Title: USE OF GRANULAR MATERIALS BASED ON PYROGENICALLY PRODUCED SILICON DIOXIDE IN PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The use of granular materials based on pyrogenically produced silicon dioxide in pharmaceutical compositions, the pharmaceutical compositions per se, as well as an adsorbate consisting of the granular material and at least one further substance selected from pharmaceutical active constituents and auxiliary substances, and the production of such adsorbates, are described.

USE OF GRANULAR MATERIALS BASED ON PYROGENICALLY PRODUCED SILICON DIOXIDE IN PHARMACEUTICAL COMPOSITIONS

The present invention relates to the use of granular materials of pyrogenic silicic acid in pharmaceutical compositions. The granular materials are used in this connection in particular as carriers of pharmaceutical active constituents and/or auxiliary substances.

Medicament compositions contain in addition to the actual active constituent a number of further constituents, the so-called auxiliary substances or adjuvants, in order to convert the active constituent into suitable preparations that are effective at the desired point of use. A problem with many medicaments is their low solubility in water, resulting in a poor bioavailability and thereby often in an inadequate efficacy. In order to increase their solubility they may be adsorbed on suitable matrices having a high surface area. Pyrogenic silicic acids for example are suitable for this purpose, and are characterised by a high purity and inert behaviour compared to other active constituents and auxiliary substances. They also adsorb numerous medicaments reversibly. Pyrogenic silicic acids correspond to the pharmacopoeia monographs for highly dispersed silicon dioxide (for example European Pharmocopoeia Monograph No. 437) and may be used without any restrictions in pharmaceutical products.

It is known that for example by applying ethinyl oestradiol to pyrogenic silicic acid, its release rate can be significantly improved (product leaflet "Pigments" No. 19, Degussa AG). For example, the sorbate of 5.2 mg

of this active constituent on 100 mg of pyrogenic silicic acid (AEROSIL 200, Degussa AG) on contact with water releases so much active constituent that a supersaturated solution is formed. An equivalent amount of the pure active constituent reaches the saturation equilibrium value of 1.1 mg/100 ml only after shaking over several days.

Numerous further AEROSIL 200 sorbates exhibit an improved active constituent release behaviour, for example those of griseofulvin (H. Rupprecht, M.J. Biersack, G. Kindl, Koll.-ZZ. Polym. 252 (1974) 415), indomethacin, aspirin, sulfaethidole, reserpine, chloramphenicol, oxolinic acid, probucol and hydrochlorothiazide (D.C. Monkhouse, J.L. Lach, J. Pharm. Sci., 57 (1968) 2143). Also, digitoxin-silicic acid matrices are characterised by an increased bioavailability compared to the pure active constituent (H. Flasch, B. Asmussen, N. Heinz, Arzneim.-Forschung/ Drug. Res. 28 (1978) 326).

In addition to the improvement in the bioavailability of sparingly soluble medicaments, carrier materials such as pyrogenic silicic acid may also be used in order to protect active constituents against environmental influences such as for example atmospheric oxygen, light or moisture and thereby stabilise them. For example, A.Y Gore et al. in J. Pharm. Sci. 68 (1979) 197 describe the stabilisation of acetylsalicylic acid against hydrolysis by means of highly dispersed silicic acid. A targeted or delayed release of active constituent may also be achieved by adsorption on a carrier.

Pyrogenic silicic acids act however not only as carriers for active constituents, but may also be used in order to convert liquid or pasty active constituents into flowable powders. In this connection the active constituents are stored in the void volumes of the pyrogenic silicic acid aggregates. The powders that are thereby produced may be processed further into widely differing medicament forms, such as for example tablets, capsules, ointments, creams or suppositories (product leaflet "Pigments" No. 49, Degussa AG).

Pyrogenic silicic acid may also be used as an antiblocking agent, disintegration accelerator, suspension stabiliser and consistency regulator in tablets, capsules, suppositories, ointments and aerosols. Further possible uses of pyrogenic silicic acid as a pharmaceutical auxiliary substance are described in Technichal Information Leaflet No. 1237 "AEROSIL 200 Pharma - A versatile excipient for the pharmaceutical industry", Degussa AG.

However, the use of pyrogenic silicic acids employed hitherto in medicament preparations does have some disadvantages. For example, a considerable amount of dust is formed during processing, which necessitates a complicated and expensive handling procedure. Furthermore available pyrogenic silicic acid has a relatively low bulk density and tamped density and is therefore bulky to transport and store. Also, available adsorbates of pyrogenic silicic acid and a medicament often have an insufficient flowability and an unknown active constituent release behaviour on account of a very broad grain size distribution dependent on their processing.

The replacement of pyrogenic silicic acid by precipitated silicic acids or silica gels is possible only to a limited extent since their purity is often not sufficient. In addition to a relatively high salt and water content contamination by germs cannot be reliably ruled out since these products are generally produced at temperatures below 100°C.

The object of the present invention is accordingly to provide an auxiliary substance for use in pharmaceutical compositions that does not exhibit the aforementioned disadvantages and also satisfies the stringent requirements of the pharmaceutical industry as regards purity and product safety.

This object is achieved by the use of a granular material based on pyrogenically produced silicon dioxide in a pharmaceutical composition. The present invention also provides a pharmaceutical composition that contains a granular material based on pyrogenically produced silicon dioxide and at least one pharmaceutical active constituent. In addition the present invention is directed to an adsorbate consisting of a granular material based on pyrogenically produced silicon dioxide and at least one further substance selected from pharmaceutical active constituents and auxiliary substances, and to the production of such adsorbates.

Preferably the granular material based on pyrogenically produced silicon dioxide has a mean grain diameter of 10 to 120 µm and a BET surface of 40 to 400 m^2/g (determination according to DIN 66 131 with nitrogen).

Preferably the silicon dioxide granular material exhibits the following physicochemical characteristic data, which are determined as described in EP PS 0 725 037:

Pore volume:	0.5 to 2.5 ml/g
Pore size distribution:	less than 5% of the overall pore volume has a pore diameter of less than 5 nm, the remainder being mesopores and macropores
pH value:	3.6 to 8.5
Tamped density:	220 to 700 g/l.

A suitable granular material for the use according to the invention and its production is described for example in EP OS 0 727 037.

Preferably the granular material may exhibit mesopores and macropores, the volume of the mesopores accounting for 10 to 80% of the total volume. The particle size distribution of the granular material is preferably 80 vol.% greater than 8 µm and 80 vol.% less than 96 µm. The proportion of pores smaller than 5 µm may in a preferred embodiment of the invention be at most 5% referred to the total pore volume.

The granular material used according to the invention may be produced for example by dispersing in water pyrogenically produced silicon dioxide, preferably silicon dioxide produced by means of flame hydrolysis from silicon tetrachloride, following which the granular material is spray dried and optionally heat treated at a temperature of 150° to 1,100°C for a period of 1 to 8 hours.

The dispersion in water preferably has a concentration of silicon dioxide of 5 to 25 wt.%, more preferably 5 to about 19.9 wt.%. The spray drying may be carried out at a temperature of 200° to 600°C, in which connection rotary-disc atomisers or nozzle atomisers may be used. The heat treatment of the granular material may be carried out under fixed bed conditions, for example in chamber furnaces, as well as under fluidised bed conditions, for example rotary tubular dryers.

The pyrogenic silicon dioxide serving as starting material is produced by feeding a volatile silicon compound through a nozzle into a detonating gas flame of hydrogen and air. Silicon tetrachloride is used in most cases. This substance hydrolyses under the influence of the water produced in the detonating gas reaction, to form silicon dioxide and hydrochloric acid. After leaving the flame the silicon dioxide enters a so-called coagulation zone in which the silicon dioxide primary particles and primary aggregates agglomerate. The product present as a form of aerosol in this stage is separated from the gaseous accompanying substances in cyclones and is then post-treated with moist hot air. The residual hydrochloric acid content can be reduced to below 0.025% by this process.

The granular materials based on pyrogenically produced silicon dioxide may also be silanised. The carbon content of the granular material is then preferably 0.3 to 15.0 wt.%. Halogenated silantes, alkoxysilanes, silazanes and/or siloxanes may be used for the silanisation.

The following substances in particular may be used as halogenated silanes:

halogenated organosilanes of the type $X_3Si(C_nH_{2n+1})$

X = Cl, Br

n = 1 - 20

halogenated organosilanes of the type $X_2(R')Si(C_nH_{2n+1})$

X = Cl, Br

R' = Alkyl

n = 1 - 20

halogenated organosilanes of the type $X(R')_2Si(C_nH_{2n+1})$

X = Cl, Br

R' = Alkyl

n = 1 - 20

halogenated organosilanes of the type $X_3Si(CH_2)_m-R'$

X = Cl, Br

m = 0.1 - 20

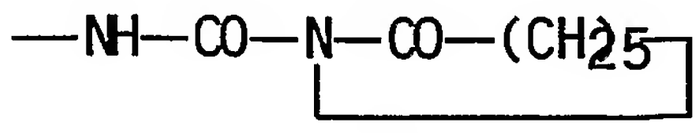
R' = Alkyl, aryl (e.g. $-C_6H_5$)

$-C_4F_9$, $-OCF_2-CHF-CF_3$, $-C_6F_{13}$, $-O-CF_2-CHF_2$

$-NH_2$, $-N_3$, $-SCN$, $-CH=CH_2$,

$-OOC(CH_3)C=CH_2$

$-OCH_2-CH(O)CH_2$



$-NH-COO-CH_3$, $-NH-COO-CH_2-CH_3$, $-NH-(CH_2)_3Si(OR)_3$

$-S_x-(CH_2)_3Si(OR)_3$

halogenated organosilanes of the type $(R)X_2Si(CH_2)_m-R'$

X = Cl, Br

R = Alkyl

m = 0.1 - 20

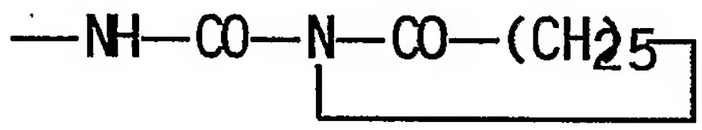
R' = Alkyl, aryl (e.g. $-C_6H_5$)

$-C_4F_9$, $-OCF_2-CHF-CF_3$, $-C_6F_{13}$, $-O-CF_2-CHF_2$

$-NH_2$, $-N_3$, -SCN, $-CH=CH_2$,

$-OOC(CH_3)C = CH_2$

$-OCH_2-CH(O)CH_2$



$-NH-COO-CH_3$, $-NH-COO-CH_2-CH_3$, $-NH-(CH_2)_3Si(OR)_3$

$-S_x-(CH_2)_3Si(OR)_3$

halogenated organosilanes of the type $(R)_2X\ Si(CH_2)_m-R'$

X = Cl, Br

R = Alkyl

m = 0.1 - 20

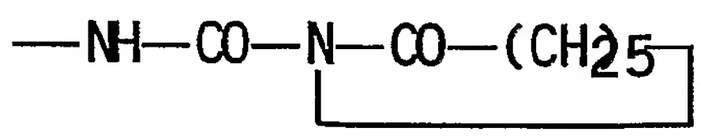
R' = Alkyl, aryl (e.g. $-C_6H_5$)

$-C_4F_9$, $-OCF_2-CHF-CF_3$, $-C_6F_{13}$, $-O-CF_2-CHF_2$

$-NH_2$, $-N_3$, -SCN, $-CH=CH_2$,

$-OOC(CH_3)C = CH_2$

$-OCH_2-CH(O)CH_2$



$-NH-COO-CH_3$, $-NH-COO-CH_2-CH_3$, $-NH-(CH_2)_3Si(OR)_3$

$-S_x-(CH_2)_3Si(OR)_3$

The following substances in particular may be used as alkoxysilanes:

organosilanes of the type $(RO)_3Si(C_nH_{2n+1})$

R = Alkyl

n = 1 - 20

organosilanes of the type $R'_x(RO)_ySi(C_nH_{2n+1})$

R = Alkyl

R' = Alkyl

n = 1 - 20

x+y = 3

x = 1.2

y = 1.2

organosilanes of the type $(RO)_3Si(CH_2)_m-R'$

R = Alkyl

m = 0.1 - 20

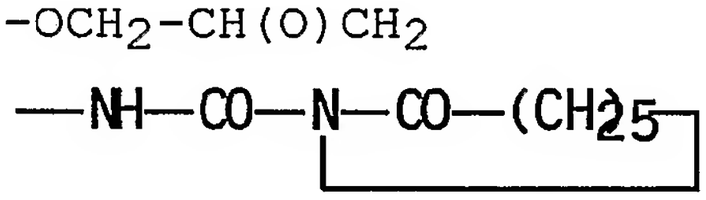
R' = Alkyl, aryl (e.g. $-C_6H_5$)

$-C_4F_9$, $OCF_2-CHF-CF_3$, $-C_6F_{13}$, $-O-CF_2-CHF_2$

$-NH_2$, $-N_3$, $-SCN$, $-CH=CH_2$,

$-OOC(CH_3)C = CH_2$

$-OCH_2-CH(O)CH_2$



$-NH-COO-CH_3$, $-NH-COO-CH_2-CH_3$, $-NH-(CH_2)_3Si(OR)_3$

$-S_x-(CH_2)_3Si(OR)_3$

organosilanes of the type $(R")_x(RO)_ySi(CH_2)_m-R'$

R" = Alkyl

x+y = 2

x = 1.2

y = 1.2

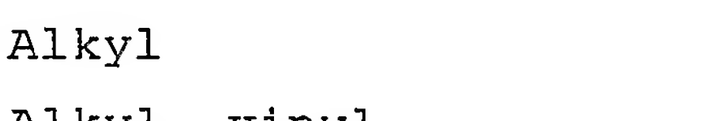
R' = Alkyl, aryl (e.g. $-C_6H_5$)

$-C_4F_9$, $-OCF_2-CHF-CF_3$, $-C_6F_{13}$, $-O-CF_2-CHF_2$

$-NH_2$, $-N_3$, -SCN, $-CH=CH_2$,

$-OOC(CH_3)C = CH_2$

$-OCH_2-CH(O)CH_2$



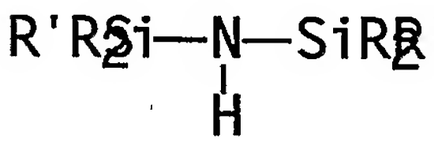
$-NH-COO-CH_3$, $-NH-COO-CH_2-CH_3$, $-NH-(CH_2)_3Si(OR)_3$

$-S_x-(CH_2)_3Si(OR)_3$

The silane Si 108 [$(CH_3O)_3$-Si-C_8H_{17}] trimethoxyoctylsilane may preferably be used as silanisation agent.

The following substances in particular may be used as silazanes:

Silazanes of the type:



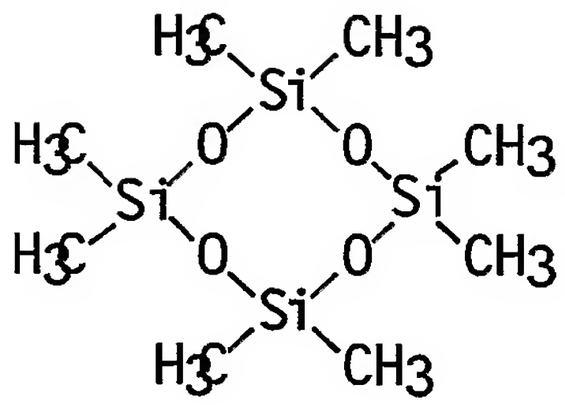
R = Alkyl

R' = Alkyl, vinyl

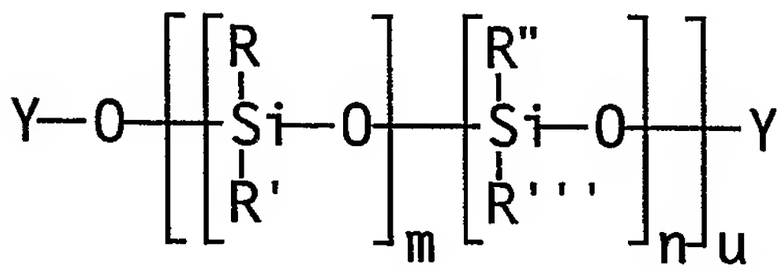
as well as for example hexamethyldisilazane.

The following substances in particular may be used as siloxanes:

cyclic polysiloxanes of the type D 3, D 4, D 5, e.g. octamethylcyclotetrasiloxane = D 4



polysiloxanes and/or silicone oils of the type:



R = Alkyl, aryl, $(CH_2)_n - NH_2$, H

R' = Alkyl, aryl, $(CH_2)_n - NH_2$, H

R'' = Alkyl, aryl, $(CH_2)_n - NH_2$, H

R''' = Alkyl, aryl, $(CH_2)_n - NH_2$, H

Y = CH_3, H, C_nH_{2n+1} where n=1-20

Y = $Si(CH_3)_3$, $Si(CH_3)_2H$

$Si(CH_3)_2OH$, $Si(CH_3)_2(OCH_3)$

$Si(CH_3)_2(C_nH_{2n+1})$ where n=1-20

m = 0,1,2,3,...∞

n = 0,1,2,3,...∞

u = 0,1,2,3,...∞

The silanisation may be carried out by spraying the granular material with the silanisation agent, which may optionally be dissolved in an organic solvent, for example ethanol, and then thermally treating the mixture at a temperature of 105° to 400°C for a period of 1 to 6 hours.

An alternative method of silanising the granular materials involves treating the granular material with the silanisation agent in vapour form and then thermally

treating the mixture at a temperature of 200° to 800°C for a period of 0.5 to 6 hours. The thermal treatment may be carried out under a protective gas, such as for example nitrogen.

The silanisation may be carried out continuously or batchwise in heatable mixers and dryers with spray devices. Suitable types of apparatus include for example ploughshare mixers, plate dryers, fluidised-bed dryers or turbulent-layer dryers.

The physicochemical parameters of the granular materials, such as the specific surface, grain size distribution, pore volume, tamped density and silanol group concentration, pore distribution and pH value may be altered within the specified limits by varying the starting substances, spraying conditions, heat treatment and silanisation.

The granular materials of pyrogenic silicon dioxide may be used according to the invention in any suitable solid, semi-solid or liquid medicament forms, preferably for oral and/or topical applications, for example in suspensions, emulsions, aerosols, ointments, creams, gels, pastes, suppositories, sticks, powders, topical powders, granules, tablets, pastilles, sugar-coated pills, film-coated tablets, hard gelatin capsules, soft gelatin capsules, extrudates, microcapsules or microspheres. Particularly preferred are solid medicament forms such as for example powders, granules, tablets and capsules. The expression "pharmaceutical composition" also covers within the scope of the present invention precursors and intermediates used for the production of granules, tablets, capsules,

suspensions, dry ointments and dry drops. Such precursors and intermediates may for example also be in the form of a powder, granular material or extrudate.

Methods for the production of solid, semi-solid and liquid medicament forms are known and are described in numerous publications and textbooks relating to pharmaceutical technology, cf. for example K.H. Bauer, K.-H. Frömming, C. Führer, Lehrbuch der pharmazeutischen Technologie, 6th Edition, Wissenschaftliche Verlagsgesellschaft mbH Stuttgart 1999.

The silicon dioxide granular material may be used in combination with any arbitrary pharmaceutical active constituent. The following may be mentioned by way of example:

α-proteinase inhibitor, abacavir, abciximab, acarbose, acetylsalicylic acid, acyclovir, adenosine, albuterol, aldesleukin, alendronate, alfuzosin, alosetrone, alprazolam, alteplase, ambroxol, amifostine, amiodarone, amisulprid, amlodipine, amoxicillin, amphetamine, amphotericin, ampicillin, amprenavir, anagrelide, anastrozole, ancrod, anti-haemophilia factor, aprotinin, atenolol, atorvastatin, atropine, azelastine, azithromycin, azulene, barnidipin, beclomethasone, benazepril, benserazide, beraprost, betamethasone, betaxolol, bezafibrate, bicalutamide, bisabolol, bisoprolol, botulinum toxin, brimonidine, bromazepam, bromocriptine, budesonide, bupivacaine, bupropion, buspirone, butorphanol, cabergoline, calcipotriene, calcitonin, calcitriol, camphor, candesartan, candesartan cilexetil, captopril, carbamazepine, carbidopa, carboplatin, carvedilol, cefaclor, cefadroxil, cefaxitin,

cefazolin, cefdinir, cefepime, cefixime, cefmetazole, cefoperazone, cefotiam, cefoxopran, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftriaxone, cefuroxime, celecoxib, celiprolol, cephalexin, cerivastatin, cetirizine, chloramphenicol, cilastatin, cilazapril, cimetidine, ciprofibrate, ciprofloxacin, cisapride, cisplatin, citalopram, clarithromycin, clavulanic acid, clindamycin, clomipramine, clonazepam, clonidine, clopidogrel, clotrimazole, clozapine, cromolyn, cyclophosphamide, cyclosporine, cyproterone, dalteparin, deferoxamine, desogestrel, dextroamphetamine, diazepam, diclofenac, didanosine, digitoxin, digoxin, dihydroergotamine, diltiazem, diphtheria protein, diphtheria toxoxide, divalproex, dobutamine, docetaxel, dolasetron, donepezil, dornase-α, dorzolamide, doxazosin, doxifluridin, doxorubicin, dydrogesterone, ecabet, efavirenz, enalapril, enoxaparin, eperisone, epinastin, epirubicin, eptifibatide, erythropoietin-α, erythropoietin-β, etanercept, ethinyl oestradiol, etodolac, etoposide, factor VIII, famciclovir, famotidine, faropeneme, felodipine, fenofibrate, fenoldopam, fentanyl, fexofenadin, filgrastim, finasteride, flomoxef, fluconazole, fludarabine, flunisolide, flunitrazepam, fluoxetine, flutamide, fluticasone, fluvastatin, fluvoxamine, follitropin-α, follitropin-β, formoterol, fosinopril, furosemide, gabapentin, gadodiamide, ganciclovir, gatifloxacin, gemcitabine, gestoden, glatiramer, glibenclamide, glimepiride, glipizide, glyburide, goserelin, granisetron, griseofulvin, hepatitis B antigen, hyaluronic acid, hycosin, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, hydroxychloroquine, hylan G-F 20, ibuprofen, ifosfamide,

imidapril, imiglucerase, imipenem, immunoglobulin, indinavir, indomethacin, infliximab, insulin, insulin human, insulin Lispro, insulin aspart, interferon β, interferon α, iodine 125, iodixanol, iohexol, iomeprol, iopromid, ioversol, ioxoprolen, ipratropium, ipriflavone, irbesartan, irinotecan, isosorbide, isotretinoin, isradipine, itraconazole, potassium chlorazepate, potassium chloride, ketorolac, ketotifen, whooping cough vaccine, coagulation factor IX, lamivudine, lamotrigine, lansoprazole, latanoprost, leflunomide, lenograstim, letrozole, leuprolide, levodopa, levofloxacin, levonorgestrel, levothyroxine, lidocaine, linezolid, lisinopril, lopamidol, loracarbef, loratadine, lorazepam, losartan, lovastatin, lysineacetylsalicylic acid, manidipin, mecobalamin, medroxyprogesterone, megestrol, meloxicam, menatetrenone, meningococcus vaccine, menotropine, meropenem, mesalamine, metaxalone, metformin, methylphenidate, methylprednisolone, metoprolol, midazolam, milrinone, minocycline, mirtazapine, misoprostol, mitoxantrone, moclobemid, modafinil, mometasone, montelukast, morniflumat, morphine, moxifloxacin, mycophenolate, nabumetone, nadroparin, naproxen, naratriptan, nefazodone, nelfinavir, nevirapine, niacin, nicardipine, nicergoline, nifedipine, nilutamide, nilvadipine, nimodipine, nitroglycerin, nizatidine, norethindrone, norfloxacin, octreotide, olanzapine, omeprazole, ondansetron, orlistate, oseltamivir, oestradiol, oestrogens, oxaliplatin, oxaprozin, oxolinic acid, oxybutynin, paclitaxel, palivizumab, pamidronate, pancrelipase, panipenem, pantoprazol, paracetamol, paroxetine, pentoxifylline, pergolide, phenytoin, pioglitazon, piperacillin, piroxicam, pramipexole,

pravastatin, prazosin, probucol, progesterone, propafenone, propofol, propoxyphene, prostaglandin, quetiapine, quinapril, rabeprazol, raloxifene, ramipril, ranitidine, repaglinide, reserpine, ribavirin, riluzole, risperidone, ritonavir, rituximab, rivastigmin, rizatriptan, rofecoxib, ropinirol, rosiglitazone, salmeterol, saquinavir, sargramostim, serrapeptase, sertraline, sevelamer, sibutramin, sildenafil, simvastatin, somatropine, sotalol, spironolactone, stavudin, sulbactam, sulfaethidole, sulfamethoxazole, sulfasalazin, sulpirid, sumatriptan, tacrolimus, tamoxifen, tamsulosin, tazobactam, teicoplanin, temocapril, temozolomid, tenecteplase, tenoxicam, teprenon, terazosin, terbinafine, terbutaline, tetanus toxoid, tetrabenazine, tetrazepam, thymol, tiagabine, tibolon, ticarcillin, ticlopidine, timolol, tirofiban, tizanidine, tobramycin, tocopheryl nicotinate, tolterodine, topiramate, topotecan, torasemid, tramadol, trandolapril, trastuzumab, triamcinolone, triazolam, trimebutin, trimethoprim, troglitazone, tropisetrone, tulobuterol, unoproston, urofollitropine, valacyclovir, valproic acid, valsartan, vancomycin, venlafaxine, verapamil, verteporfin, vigabatrin, vinorelbine, vinpocetine, voglibose, warfarin, zafirlukast, zaleplon, zanamivir, zidovudine, zolmitriptan, zolpidem, zopiclone and their derivatives. Pharmaceutical active constituents are however also understood to include other substances such as vitamins, provitamins, essential fatty acids, extracts of plant and animal origin and oils of plant and animal origin.

Further constituents of the pharmaceutical compositions may include conventional auxiliary substances such as for example antioxidants, binders, emulsifiers, colouring agents, film-forming agents, fillers, odoriferous substances, flavouring substances, gel-forming agents, preservatives, solvents, oils, powder bases, ointment bases, acids and salts for the formulation, replenishment and production of pharmaceutical compositions, lubricants, release agents, suppository bases, suspension stabilisers, sweetening agents, effervescent gases, emollients and sugar substitutes.

Plant medicament preparations and homeopathic preparations are also included among the pharmaceutical compositions in which the silicon dioxide granular materials may be used.

The pharmaceutical compositions according to the invention may also include so-called retard and depôt medicament forms with controlled release of active constituent. Moreover the pharmaceutical compositions according to the invention may also be part of therapeutic systems such as for example therapeutic systems for topical application and transdermal therapeutic systems.

In a preferred embodiment the silicon dioxide granular material based on pyrogenic silicic acid serves as a carrier for pharmaceutical active constituents and/or auxiliary substances. The present invention is accordingly also directed to an adsorbate of the aforedescribed silicon dioxide granular material and at least one of these substances.

The expression "adsorbate" as used in the present specification covers not only the adsorption of a substance on the surface of the silicon dioxide, but also in the pores, as well as the "incorporation" in the void volumes. The term "adsorbate" may also mean that silicon dioxide granular material or fragments thereof coat solids particles or liquid droplets of the material. In the latter case the forces of attraction between the particles and/or droplets are reduced and for example the flow behaviour is improved and/or the coalescence of droplets is prevented.

In principle the silicon dioxide granular material may act as a carrier for any suitable pharmaceutical active constituent or auxiliary substance; preferred however are adsorbates containing the aforementioned active constituents and auxiliary substances and/or their mixtures. Of the pharmaceutical auxiliary substances, there are preferably adsorbed on the silicon dioxide granular material odoriferous substances, flavouring agents or colouring agents. The odoriferous substances and flavouring agents may be of natural, i.e. plant or animal origin, as well as synthetic, i.e. fully synthetic or semi-synthetic origin.

Examples of plant odoriferous substances include ethereal oils and resinoids. Examples of animal odoriferous substances that may be mentioned include musk, civet, castoreum and ambergris. The fully synthetic odoriferous substances include those that have an odoriferous prototype in nature, as well as pure fantasy compositions. Semi-synthetic odoriferous substances are understood to be

those that can be isolated from natural fragrances and then chemically converted.

Also, the colouring agents may be natural or synthetic colouring agents, and organic or inorganic compounds.

Granular materials formed from pyrogenic silicic acid are suitable in particular as carriers for substances:

- whose release behaviour is improved by application to a high surface area carrier substance, for example in the case of sparingly water-soluble substances;
- whose release behaviour is too quick, for example in the case of retard formulations;
- that are liquid or pasty and are therefore e.g. difficult to meter and/or handle;
- that can be processed only with difficulty, for example as a result of too low a melting point;
- whose flow behaviour is insufficient for further processing, for example for producing tablets and capsules;
- that are readily volatile;
- that are sensitive to external conditions such as for example atmospheric oxygen, light, moisture, acids (gastric juice) or bases (intestinal fluid).

Numerous active constituents can be stabilised in this way, such as for example acetylsalicylic acid; atropine; azulene; bisabolol; camphor; chloramphenicol; hydrocortisone and its derivatives, such as for example hydrocortisone-17-valerate, prostaglandins; thymol; (pro)vitamins and their derivatives, such as for example vitamin A and E; unsaturated fatty acids, specifically

essential fatty acids such as for example gamma-linolenic acid, oleic acid, eicosapentenoic acid and docosahexenoic acid; extracts of animal and plant origin and oils of animal and plant origin, such as for example fish oils, evening primrose oil, borage oil, currant seed oil and cod liver oil.

Sparingly soluble substances whose release behaviour can be improved by application to the granular materials formed from pyrogenic silicic acid include for example indomethacin, sulfaethidole, reserpine, griseofulvin, probucol and oxolinic acid. Also, the release behaviour of per se readily soluble substances such as for example hydrochlorothiazide, chloramphenicol and acetylsalicylic acid can be improved further in this way.

An example of an active constituent that is difficult to process or cannot be processed at all by conventional methods is ibuprofen, above all S-ibuprofen, which has a melting point of only 52°C. On account of the low melting point granulation processes apart from as an adsorbate according to the invention are hardly feasible. Moreover substances that for example sinter during the tabletting form preferred adsorbates within the context of the present invention with the silicon dioxide granular material.

The quantitative ratio of substance to silicon dioxide granular material in the adsorbate may be chosen as desired depending on the properties of the substance and the requirements that the end product has to meet. However, preferably 0.001 to 200 g of substance,

particularly preferably 10 to 150 g of substance, are used per 100 g of silicon dioxide granular material.

Various procedures may be employed in order to apply and/or adsorb the desired active constituents and/or auxiliary substances on the silicon dioxide granular material. An exemplary process for the production of the adsorbate according to the invention comprises the following steps:

(a) melting of the substance(s) to be adsorbed, selected from pharmaceutical active constituents and auxiliary substances, or distribution, i.e. dissolution, suspension or emulsification, of the latter in a solvent;

(b) mixing the granular material based on pyrogenically produced silicon dioxide with the mixture from step (a); and

(c) optionally removal of the solvent.

The term "solvent" also includes mixtures of several different solvents. It is also understood that substances already liquid at room temperature can be subjected without prior processing to the mixing in step (b) since in this case the "melting process" has already taken place. The mixing step (b) may be carried out either by adding the mixture from step (a) to the silicon dioxide granular material, for example by spraying, or vice versa. In both cases the addition may take place in one amount or in portions. The duration of the mixing in step (b) depends above all on the adsorption behaviour of the substance to be adsorbed on the silicic acid surface. If a solvent is present, step (a) and step (b) are carried out at a temperature that is between the freezing point

and boiling point of the solvent. The excess solvent that may be present is removed in step (c), preferably at elevated temperature and/or reduced pressure.

The removal of the solvent in step (c) may also be effected by spray drying or fluidised bed drying, a forming being carried out at the same time. In the case of a melt containing granular material the forming process may appropriately comprise an extrusion.

Granular materials formed from pyrogenic silicic acids may however also be used for the production of pharmaceutical preparations without their simultaneously acting as carriers and/or adsorption agents. In this case they can in particular complement or replace the conventional pyrogenic silicic acids that have been established in pharmaceutical practice for many years. For example, granular materials of pyrogenic silicic acids may above all improve the production and properties of solid medicament forms. Also, they may advantageously be employed in the production of extrudates and replace for example other established auxiliary substances such as cellulose or polymers.

The advantages of the granular materials based on pyrogenically produced silicon dioxide compared to the known non-granulated pyrogenic silicic acids lie above all in the higher bulk density and tamped density, improved flowability, narrower grain size distribution, and dust-free processing. In addition tablets produced therefrom have a higher mechanical stability and an improved disintegration behaviour.

The invention will now be described in more detail with the aid of examples.

Reference examples A and B: production of the granular materials based on pyrogenically produced silicon dioxide

The pyrogenically produced silicon dioxides AEROSIL 90 and AEROSIL 300, both of which are commercially obtainable from Degussa AG, are used as starting compounds.

The pyrogenically produced silicon dioxide is dispersed in fully deionised water. In this connection dispersing equipment is used that operates according to the rotor/stator principle. The suspensions that are formed are spray dried. The deposition of the finished product is carried out using a filter or cyclone. The heat treatment of the spray-dried granular materials is carried out in muffle furnaces.

The production parameters are given in Table 1.

Table 1

Reference Example	A	B
Starting SiO_2	AEROSIL 90	AEROSIL 300

Data for the spray drying		
Amount H_2O (kg)	100	100
Amount SiO_2 (kg)	1.5	10
Atomisation with	1-substance nozzle	disc
operating temp. (°C)	358	380
Exhaust air temp. (°C)	105	105
Deposition	filter	filter
Physicochemical data		
BET surface (m^2/g)	87	279
Grain size d^{50} (µm)	25	27.9
Tamped volume (g/l)	258	28.9
pH value	4.7	4.6
Carbon content %	-	-

Examples 1a and 1b: SiO_2 granular materials containing vitamin E acetate

50.0 g of the granular materials produced in reference examples A and B from AEROSIL 90 (Example 1a) and from AEROSIL 300 (Example 1b) were in each case placed in a tall 600 ml capacity beaker and 50.0 g of vitamin E acetate (from BASF) was stirred in in portions using a spatula. Both granular materials quickly absorbed the oily liquid, did not form any dust and did not produce an electrostatic charge. The total amount of the vitamin E acetate could be processed within ten minutes. The dry mixtures were then screened through a sieve having a mesh width of 0.75 mm and allowed to stand overnight.

The flow score and shaking cone height were determined as described in the Technical Information Leaflet "Pigments" No. 31 "AEROSIL zur Verbesserung des Fließverhaltens pulverförmiger Substanzen" from Degussa AG. The bulk

density and tamped density are according to DIN Norm 66131. The data are summarised in Table 2.

Comparison examples 1a*-c*: Vitamin E acetate on non-granulated pyrogenic SiO_2 (AEROSIL 90, 200 and 300, Degussa AG)

50.0 g of AEROSIL 90 (comparison example 1a*), AEROSIL 300 (comparison example 1b*) and AEROSIL 200 (comparison example 1c*) were placed in a tall 600 ml capacity beaker and 50.0 g of vitamin E acetate (BASF) were stirred in in portions using a spatula. The pyrogenic silicon dioxides absorbed the oily substance only very slowly, produced a large amount of dust and developed an electrostatic charge. A time of ca. two hours was needed to incorporate the total amount of vitamin E acetate. As in Example 1, the dry mixtures were then screened and allowed to stand overnight.

The flow score, shaking cone height, bulk and tamped densities were determined as in Example 1 and are also shown in Table 2.

Table 2

	Examples		Comparison Examples		
	1a	1b	1a*	1b*	1c*
Employed SiO_2	AEROSIL 90 Granulate	AEROSIL 300 Granulate	AEROSIL 90	AEROSIL 300	AEROSIL 200
Flow score	1	1	5-6	5	4-5
Shaking cone height	1.35	1.20	3.00	2.90	4.50

(cm)					
Bulk density (g/l)	431	454	227	158	160
Tamped density (g/l)	500	568	290	215	222

The flow score and shaking cone height of the adsorbates on SiO_2 granular materials (Examples 1a and 1b) demonstrated a very good flow behaviour of both products. All three adsorbates of the comparison examples showed a poor flow behaviour. Also, the bulk and tamped densities were low and were not sufficient for many applications.

Examples 2a and 2b: Hard gelatin capsules containing vitamin E acetate (SiO_2 granular material)

Hard gelatin capsules of size 1 (Scherer, empty weight 71 - 78 mg) were filled with the vitamin E acetate adsorbates from Example 1 using a capsule-filling device (Simplex type, Raebiger). The mean capsule weights (mean value of 20 randomly selected capsules) are included together with the standard deviations of the weight in Table 3.

Comparison examples 2a*-c*: Hard gelatin capsules containing vitamin E acetate (non-granulated SiO_2)

Hard gelatin capsules were filled as described in Example 2 with the vitamin E acetate adsorbates of comparison example 1*. The results are also shown in Table 3.

Table 3

	Examples		Comparison Examples		
	2a	2b	2a*	2b*	2c*
Employed SiO_2	AEROSIL 90 Granulate	AEROSIL 300 Granulate	AEROSIL 90	AEROSIL 300	AEROSIL 200
Capsule weight (mg)	271	284	165	110	139
Relative standard deviation (%)	0.9	1.2	7.9	4.2	8.1

The capsules produced in Example 2 had a significantly higher weight that those of comparison example 2*, and therefore contained more active constituent. Also, in Example 2 the relative standard deviations of the capsule weight were substantially less than in comparison example 2*. The uniformity of the capsule weight is an important requirement of all Pharmacopoeias.

Example 3: SiO_2 granular material containing acetylsalicylic acid and hard gelatin capsules produced therefrom

30 g of the granular material consisting of AEROSIL 300 produced in reference example B were added to a solution of 60 g of acetylsalicylic acid (Caelo) in 500 ml of acetone and the resultant mixture was stirred for two hours at room temperature with a magnetic stirrer. The acetone was then completely distilled off in a rotary

evaporator at a water bath temperature of 40°C, and the resultant solid was dried for two hours at 45°C in a drying cabinet and then allowed to stand overnight in a desiccator. The product was screened through a 0.75 mm sieve before the characterisation and further processing. Hard gelatin capsules were filled with the product according to the procedure of Example 2. The analytical data are summarised in Table 4.

Comparison example 3*: acetylsalicylic acid on non-granulated pyrogenic SiO_2

Comparison example 3 was carried out similarly to Example 3. AEROSIL 300 was used instead of an AEROSIL 300 granular material. The analytical data are also shown in Table 4.

Table 4

	Example 3	Comparison Example 3*
Employed SiO_2	AEROSIL 300 Granulate	AEROSIL 300
Shaking cone height (cm)	1.6	1.7
Bulk density (g/l)	347	323
Tamped density (g/l)	454	410
Mean capsule weight (mg)	232	224
Standard deviation of the capsule weight (%)	1.65	2.6

The acetylsalicylic acid adsorbate (Example 3) produced with the AEROSIL 300 granular material has a better flowability as well as a higher bulk density and tamped density than the product (comparison example 3*) produced

with AEROSIL 300. The mean capsule weight is also correspondingly higher in Example 3 than in comparison example 3*.

Example 4: Acetylsalicylic acid tablets (SiO_2 granular material)

The product of Example 3 was used to produce tablets according to the formulation in Table 5.

Table 5

Starting Substance	Commercial Name, Manufacturer	Amount per 600 mg Tablet (mg)	Content (wt.%)
Acetylsalicylic acid adsorbate	from Example 3	500.00	83.33
Powdered cellulose	ELCEMA P 100 (Rettenmaier)	62.2	10.4
Corn starch	Corn starch (Caelo)	30.00	5.00
Stearic acid	Stearic acid (Merck)	6.00	1.00
Highly dispersed silicon dioxide	AEROSIL 200 (Degussa AG)	1.8	0.3

To prepare a 200 g batch the powdered starting materials were weighed out in the specified sequence to an accuracy of 0.01 g and mixed by hand in a closed 1000 ml wide-necked glass flask. The mixture was screened through a sieve with a mesh width of 0.75 mm, readded to the already used glass flask, and homogenised with a Turbula mixer (Bachofen) for five minutes at an average speed setting (stage 3). The resultant powder mixture was characterised similarly to Example 1.

The mixture was then compressed into tablets using an eccentric press (EKO, Korsch, punch size 11 mm, flat punch with facets). The filling of the matrix and upper punch pressure of the press were adjusted so that tablets were formed having a weight of ca. 600 mg and a fracture hardness of ca. 100 N.

The tablets were characterised as follows:

- Abrasion / friability: the rolling wear and falling wear of 10 tablets were measured with an abrasion tester (Erweka, Type TA 3) after 125 revolutions. The weight difference of the tablets before and after the test was measured.
- Disintegration: the disintegration time of 6 tablets in water at 37°C was determined using a disintegration tester (Erweka, Type ZT 31 on vibrating baskets).
- The tablet hardness was measured in each case on 10 tablets with a semi-automatic hardness tester (Erweka, TBH 30 MD).
- Mean tablet weight and standard deviation were determined in each case on 20 tablets using an analytical balance.

The analytical data are shown in Table 6.

Comparison example 4*: acetylsalicylic acid tablets (non-granulated SiO_2)

Acetylsalicylic acid tablets were produced starting from the product of comparison example 3* similarly to Example 4 with the same machine setting, and characterised. The analytical data are given in Table 6.

Table 6

	Example 4	Comparison Example 4*
Employed SiO_2	AEROSIL 300 Granulate	AEROSIL 300
Shaking cone (cm)	1.8	1.9
Bulk density (g/l)	390	367
Abrasion (%)	1.0	1.3
Disintegration (min)	<1	11
Hardness (N)	105	90
Mean tablet weight (mg)	604	532
Standard deviation of the tablet weight (%)	0.5	0.8

The powder mixture in Example 4 was more flowable compared to that in comparison example 4* and had a higher bulk density. The tablets of Example 4 were mechanically more stable than those of comparison example 4*, disintegrated more rapidly, and had a higher tablet weight as well as a smaller standard deviation of the weight.

Example 5: Paracetamol tablets (SiO_2 granular material)

Starting from the formulation in Table 7, Paracetamol tablets were produced similarly to Example 4 using an AEROSIL 300 granular material from reference example B. The analytical data are shown in Table 8.

Table 7

Starting Substance	Amt. Weighed Out (g)	Concentration (wt.%)
Paracetamol	166.60	83.3
Microcrystalline cellulose (Unitab 101 F)	25.60	12.8
Corn starch	6.00	3.0
Magnesium stearate	0.20	0.1
AEROSIL 300 granulate	1.60	0.8

Comparison example 5*: Paracetamol tablets (non-granulated SiO_2)

Paracetamol tablets were produced similarly to Example 5 with non-granulated AEROSIL 300. The analytical data are likewise shown in Table 8.

Table 8

	Example 5	Comparison Example 5*
Shaking cone height of the employed starting powder (cm)	1.9	1.7
Tablet abrasion (%)	2.8	2.6
Tablet disintegration (s)	10	< 10
Tablet hardness (N)	63.6	65.6
Tablet weight (mg)	600.5	614.3

When using AEROSIL 300 granular material (Example 5) instead of non-granulated AEROSIL 300 (comparison

example 5*), tablets were obtained having a higher mechanical stability, a more rapid disintegration, and a higher tablet weight. In addition the powder mixture used for the tabletting was more flowable (smaller shaking cone height).

CLAIMS

1. Use of a granular material based on pyrogenically produced silicon dioxide in a pharmaceutical composition.

2. Use according to claim 1, characterised in that the granular material has a mean grain diameter of 10 to 120 µm and a BET surface of 40 to 400 m^2/g (determination according to DIN 66 131 using nitrogen).

3. Use according to claim 1 or 2, characterised in that the pharmaceutical composition is present in the form of a suspension, emulsion, aerosol, ointment, cream, gel, paste, suppository, stick, powder, topical powder, granular material, tablet, pastille, sugar-coated pill, film-coated tablet, hard gelatin capsule, soft gelatin capsule, extrudate, microcapsule or a microsphere.

4. Use according to one of claims 1 to 3, characterised in that the granular material acts as a carrier for pharmaceutical active constituents and/or auxiliary substances.

5. Pharmaceutical composition containing a granular material based on pyrogenically produced silicon dioxide and at least one pharmaceutical active constituent.

6. Pharmaceutical composition according to claim 5, characterised in that the granular material has a mean grain diameter of 10 to 120 µm and a BET surface of 40 to 400 m^2/g (determined according to DIN 66 131 using nitrogen).

7. Pharmaceutical composition according to claim 5 or 6, characterised in that it furthermore contains at least one pharmaceutical auxiliary substance.

8. Pharmaceutical composition according to one of claims 5 to 7, characterised in that the pharmaceutical active constituent is selected from:
α-proteinase inhibitor, abacavir, abciximab, acarbose, acetylsalicylic acid, acyclovir, adenosine, albuterol, aldesleukin, alendronate, alfuzosin, alosetrone, alprazolam, alteplase, ambroxol, amifostine, amiodarone, amisulprid, amlodipine, amoxicillin, amphetamine, amphotericin, ampicillin, amprenavir, anagrelide, anastrozole, ancrod, anti-haemophilia factor, aprotinin, atenolol, atorvastatin, atropine, azelastine, azithromycin, azulene, barnidipin, beclomethasone, benazepril, benserazide, beraprost, betamethasone, betaxolol, bezafibrate, bicalutamide, bisabolol, bisoprolol, botulinum toxin, brimonidine, bromazepam, bromocriptine, budesonide, bupivacaine, bupropion, buspirone, butorphanol, cabergoline, calcipotriene, calcitonin, calcitriol, camphor, candesartan, candesartan cilexetil, captopril, carbamazepine, carbidopa, carboplatin, carvedilol, cefaclor, cefadroxil, cefaxitin, cefazolin, cefdinir, cefepime,

cefixime, cefmetazole, cefoperazone, cefotiam, cefoxopran, cefpodoxime, cefprozil, ceftazidime, ceftibuten, ceftriaxone, cefuroxime, celecoxib, celiprolol, cephalexin, cerivastatin, cetirizine, chloramphenicol, cilastatin, cilazapril, cimetidine, ciprofibrate, ciprofloxacin, cisapride, cisplatin, citalopram, clarithromycin, clavulanic acid, clindamycin, clomipramine, clonazepam, clonidine, clopidogrel, clotrimazole, clozapine, cromolyn, cyclophosphamide, cyclosporine, cyproterone, dalteparin, deferoxamine, desogestrel, dextroamphetamine, diazepam, diclofenac, didanosine, digitoxin, digoxin, dihydroergotamine, diltiazem, diphtheria protein, diphtheria toxoxide, divalproex, dobutamine, docetaxel, dolasetron, donepezil, dornase-α, dorzolamide, doxazosin, doxifluridin, doxorubicin, dydrogesterone, ecabet, efavirenz, enalapril, enoxaparin, eperisone, epinastin, epirubicin, eptifibatide, erythropoietin-α, erythropoietin-β, etanercept, ethinyl oestradiol, etodolac, etoposide, factor VIII, famciclovir, famotidine, faropeneme, felodipine, fenofibrate, fenoldopam, fentanyl, fexofenadin, filgrastim, finasteride, flomoxef, fluconazole, fludarabine, flunisolide, flunitrazepam, fluoxetine, flutamide, fluticasone, fluvastatin, fluvoxamine, follitropin-α, follitropin-β, formoterol, fosinopril, furosemide, gabapentin, gadodiamide, ganciclovir, gatifloxacin, gemcitabine, gestoden, glatiramer, glibenclamide, glimepiride, glipizide, glyburide, goserelin, granisetron, griseofulvin, hepatitis B antigen, hyaluronic acid, hycosin, hydrochlorothiazide,

hydrocodone, hydrocortisone, hydromorphone, hydroxychloroquine, hylan G-F 20, ibuprofen, ifosfamide, imidapril, imiglucerase, imipenem, immunoglobulin, indinavir, indomethacin, infliximab, insulin, insulin human, insulin Lispro, insulin aspart, interferon β, interferon α, iodine 125, iodixanol, iohexol, iomeprol, iopromid, ioversol, ioxoprolen, ipratropium, ipriflavone, irbesartan, irinotecan, isosorbide, isotretinoin, isradipine, itraconazole, potassium chlorazepate, potassium chloride, ketorolac, ketotifen, whooping cough vaccine, coagulation factor IX, lamivudine, lamotrigine, lansoprazole, latanoprost, leflunomide, lenograstim, letrozole, leuprolide, levodopa, levofloxacin, levonorgestrel, levothyroxine, lidocaine, linezolid, lisinopril, lopamidol, loracarbef, loratadine, lorazepam, losartan, lovastatin, lysineacetylsalicylic acid, manidipin, mecobalamin, medroxyprogesterone, megestrol, meloxicam, menatetrenone, meningococcus vaccine, menotropine, meropenem, mesalamine, metaxalone, metformin, methylphenidate, methylprednisolone, metoprolol, midazolam, milrinone, minocycline, mirtazapine, misoprostol, mitoxantrone, moclobemid, modafinil, mometasone, montelukast, morniflumat, morphine, moxifloxacin, mycophenolate, nabumetone, nadroparin, naproxen, naratriptan, nefazodone, nelfinavir, nevirapine, niacin, nicardipine, nicergoline, nifedipine, nilutamide, nilvadipine, nimodipine, nitroglycerin, nizatidine, norethindrone, norfloxacin, octreotide, olanzapine, omeprazole, ondansetron, orlistate, oseltamivir, oestradiol, oestrogens, oxaliplatin, oxaprozin, oxolinic acid,

oxybutynin, paclitaxel, palivizumab, pamidronate, pancrelipase, panipenem, pantoprazol, paracetamol, paroxetine, pentoxifylline, pergolide, phenytoin, pioglitazon, piperacillin, piroxicam, pramipexole, pravastatin, prazosin, probucol, progesterone, propafenone, propofol, propoxyphene, prostaglandin, quetiapine, quinapril, rabeprazol, raloxifene, ramipril, ranitidine, repaglinide, reserpine, ribavirin, riluzole, risperidone, ritonavir, rituximab, rivastigmin, rizatriptan, rofecoxib, ropinirol, rosiglitazone, salmeterol, saquinavir, sargramostim, serrapeptase, sertraline, sevelamer, sibutramin, sildenafil, simvastatin, somatropine, sotalol, spironolactone, stavudin, sulbactam, sulfaethidole, sulfamethoxazole, sulfasalazin, sulpirid, sumatriptan, tacrolimus, tamoxifen, tamsulosin, tazobactam, teicoplanin, temocapril, temozolomid, tenecteplase, tenoxicam, teprenon, terazosin, terbinafine, terbutaline, tetanus toxoid, tetrabenazine, tetrazepam, thymol, tiagabine, tibolon, ticarcillin, ticlopidine, timolol, tirofiban, tizanidine, tobramycin, tocopheryl nicotinate, tolterodine, topiramate, topotecan, torasemid, tramadol, trandolapril, trastuzumab, triamcinolone, triazolam, trimebutin, trimethoprim, troglitazone, tropisetrone, tulobuterol, unoproston, urofollitropine, valacyclovir, valproic acid, valsartan, vancomycin, venlafaxine, verapamil, verteporfin, vigabatrin, vinorelbine, vinpocetine, voglibose, warfarin, zafirlukast, zaleplon, zanamivir, zidovudine, zolmitriptan, zolpidem, zopiclone and their derivatives.

9. Pharmaceutical composition according to claim 7 or 8, characterised in that the pharmaceutical auxiliary substance is selected from:
antioxidants, binders, emulsifiers, colouring agents, film-forming agents, fillers, gel-forming agents, odoriferous substances, flavouring substances, preservatives, solvents, oils, powder bases, ointment bases, acids and salts for the formulation, replenishment and production of pharmaceutical compositions, lubricants, release agents, suppository bases, suspension stabilisers, sweetening agents, effervescent gases, emollients and sugar substitutes.

10. Adsorbate of a granular material based on pyrogenically produced silicon dioxide and at least one further substance selected from pharmaceutical active constituents and auxiliary substances.

11. Adsorbate according to claim 10, characterised in that the granular material has a mean grain diameter of 10 to 120 µm and a BET surface of 40 to 400 m^2/g (determination according to DIN 66 131 using nitrogen).

12. Adsorbate according to claim 10 or 11, characterised in that the pharmaceutical active constituent is selected from the active constituents specified in claim 8.

13. Adsorbate according to one of claims 10 to 12, characterised in that the pharmaceutical auxiliary

substance is selected from the auxiliary substances specified in claim 9.

14. Process for the production of an adsorbate according to one of claims 10 to 13, comprising the following steps:

(a) melting the substance(s) to be adsorbed, selected from pharmaceutical active constituents and auxiliary substances, or distribution thereof in the solvent;

(b) mixing the granular material based on pyrogenically produced silicon dioxide with the mixture from step (a); and

(c) optionally removal of the solvent.

INTERNATIONAL SEARCH REPORT

Ir ›nal Application No
PCT/EP 02/07588

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/02 A61K31/00 A61K31/60 A61K31/165 A61K31/355
A61P29/00 A61P39/06 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 217 909 B1 (STANIFORTH JOHN H ET AL) 17 April 2001 (2001-04-17)	1-14
Y	the whole document column 1, line 20-25 column 3, line 5-24 column 4, line 41-43 - line 52-56 column 5, line 1-57 column 6, line 17-37 column 8, line 5-62 column 9, line 4-10 - line 37-63 column 10, line 6,7 - line 41-60 column 11, line 6-35 - line 40-60 column 12, line 21-44 column 14, line 23 -column 15, line 36 claims 1-3,12-16; examples 1,10,13-19	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° *Special categories of cited documents :*

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the *invention*

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2003	28/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 *epo nl*, Fax: (+31–70) 340–3016	Luangkhot, N

INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/EP 02/07588

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/001664 A1 (SHERWOOD ET AL) 24 May 2001 (2001-05-24)	1-14
Y	the whole document claims 1-3,7-9,12-15,23-33,39-54,60-63 paragraphs '0002!,'0017!,'0025!,'0028!,'0032!-'0038!, '0041!,'0056!-'0059!,'0061!,'0065!,'0068!, '0069!,'0073!,'0075!,'0076! paragraphs '0079!,'0080!,'0093!-'0097!,'0101!-'0103!, '0130!,'0133!; examples 1,10,13	1-14

X	US 6 103 219 A (STANIFORTH JOHN H ET AL) 15 August 2000 (2000-08-15)	1-14
Y	the whole document claims 33-58	1-14

Y	US 5 776 240 A (MEYER JUERGEN ET AL) 7 July 1998 (1998-07-07) the whole document column 1, line 48-62 column 2, line 1-25 column 5, line 4-17 claims 1,14-16	1-14
Y	& EP 0 725 037 A (DEGUSSA) 7 August 1996 (1996-08-07) cited in the application the whole document	1-14

Y	BAUER, FRÖMMING, FÜHRER: "Pharmazeutische Technologie" 1997 , GUSTAV FISCHER , STUTTGART JENA LÜBECK ULM XP002225023 ISBN:3-437-25630-0 page 305-306 page 305, column 2, paragraph 5 -page 306, column 1, paragraph 1	1-14

INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/EP 02/07588

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6217909 B1	17-04-2001	US 6103219 A	15-08-2000
		US 5725884 A	10-03-1998
		US 5585115 A	17-12-1996
		US 2001001664 A1	24-05-2001
		US 2002142032 A1	03-10-2002
		US 6471994 B1	29-10-2002
		US 6106865 A	22-08-2000
		AU 698667 B2	05-11-1998
		AU 4759896 A	31-07-1996
		AU 708346 B2	05-08-1999
		AU 5019996 A	07-08-1996
		AU 5830399 A	06-01-2000
		BR 9605245 A	16-09-1997
		BR 9605329 A	16-09-1997
		CA 2183881 A1	18-07-1996
		CA 2183882 A1	25-07-1996
		EP 0752848 A1	15-01-1997
		EP 0749300 A1	27-12-1996
		FI 963496 A	06-11-1996
		FI 963497 A	06-11-1996
		HU 9602360 A2	28-08-1997
		HU 9602361 A2	28-08-1997
		IL 116675 A	31-10-2000
		JP 3300364 B2	08-07-2002
		JP 10500426 T	13-01-1998
		JP 10512862 T	08-12-1998
		NO 963732 A	08-11-1996
		NO 963733 A	06-09-1996
		WO 9622080 A1	25-07-1996
		WO 9621429 A1	18-07-1996
		US 5725883 A	10-03-1998
		US 5866166 A	02-02-1999
		US 5741524 A	21-04-1998
		US 5948438 A	07-09-1999
		US 5858412 A	12-01-1999
US 2001001664 A1	24-05-2001	US 6217909 B1	17-04-2001
		US 6103219 A	15-08-2000
		US 5725884 A	10-03-1998
		US 5585115 A	17-12-1996
		US 2002142032 A1	03-10-2002
		US 6471994 B1	29-10-2002
		US 6106865 A	22-08-2000
		AU 698667 B2	05-11-1998
		AU 4759896 A	31-07-1996
		AU 708346 B2	05-08-1999
		AU 5019996 A	07-08-1996
		AU 5830399 A	06-01-2000
		BR 9605245 A	16-09-1997
		BR 9605329 A	16-09-1997
		CA 2183881 A1	18-07-1996
		CA 2183882 A1	25-07-1996
		EP 0752848 A1	15-01-1997
		EP 0749300 A1	27-12-1996
		FI 963496 A	06-11-1996
		FI 963497 A	06-11-1996
		HU 9602360 A2	28-08-1997
		HU 9602361 A2	28-08-1997

INTERNATIONAL SEARCH REPORT

Inte al Application No
PCT/EP 02/07588

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2001001664 A1		IL 116675 A	31-10-2000
		JP 3300364 B2	08-07-2002
		JP 10500426 T	13-01-1998
		JP 10512862 T	08-12-1998
		NO 963732 A	08-11-1996
		NO 963733 A	06-09-1996
		WO 9622080 A1	25-07-1996
		WO 9621429 A1	18-07-1996
		US 5725883 A	10-03-1998
		US 5866166 A	02-02-1999
		US 5741524 A	21-04-1998
		US 5948438 A	07-09-1999
		US 5858412 A	12-01-1999
US 6103219 A	15-08-2000	US 5725884 A	10-03-1998
		US 5585115 A	17-12-1996
		US 6471994 B1	29-10-2002
		US 6217909 B1	17-04-2001
		US 2001001664 A1	24-05-2001
		US 2002142032 A1	03-10-2002
		US 6106865 A	22-08-2000
		AU 698667 B2	05-11-1998
		AU 4759896 A	31-07-1996
		AU 708346 B2	05-08-1999
		AU 5019996 A	07-08-1996
		AU 5830399 A	06-01-2000
		BR 9605245 A	16-09-1997
		BR 9605329 A	16-09-1997
		CA 2183881 A1	18-07-1996
		CA 2183882 A1	25-07-1996
		EP 0752848 A1	15-01-1997
		EP 0749300 A1	27-12-1996
		FI 963496 A	06-11-1996
		FI 963497 A	06-11-1996
		HU 9602360 A2	28-08-1997
		HU 9602361 A2	28-08-1997
		IL 116675 A	31-10-2000
		JP 3300364 B2	08-07-2002
		JP 10500426 T	13-01-1998
		JP 10512862 T	08-12-1998
		NO 963732 A	08-11-1996
		NO 963733 A	06-09-1996
		WO 9622080 A1	25-07-1996
		WO 9621429 A1	18-07-1996
		US 5725883 A	10-03-1998
		US 5866166 A	02-02-1999
		US 5741524 A	21-04-1998
		US 5948438 A	07-09-1999
		US 5858412 A	12-01-1999
US 5776240 A	07-07-1998	DE 19601415 A1	08-08-1996
		CA 2168677 A1	05-08-1996
		CN 1134399 A ,B	30-10-1996
		DE 59606530 D1	12-04-2001
		EP 0725037 A1	07-08-1996
		ES 2154748 T3	16-04-2001
		JP 3095989 B2	10-10-2000
		JP 8253309 A	01-10-1996

INTERNATIONAL SEARCH REPORT

Int	Application No
	PCT/EP 02/07588

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5776240 A		KR 190472 B1	01-06-1999
		PT 725037 T	31-07-2001
		SG 42921 A1	17-10-1997